REMARKS

Claims 5, 7-17 and 20-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the reply filed on 10-9-07.

Applicant's election without traverse of Group I, claims 1-4, 6, 18 and 19 in the reply filed on 10-9-07 has been acknowledged and are now pending.

Claims 3 and 19 have been amended. Claims 1-2, 4, 6 and 18 have been canceled without prejudice. New claims 28-30 have been added. Accordingly, upon entry of this amendment, claims 3, 19 and 28 - 30 shall be pending.

No new matter has been added by this amendment.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

The rejections under 35 U.S.C. § 112 are overcome

1. Claims 1-4, 6, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> The Examiner states, "The claims are drawn to prophylactic/ therapeutic and apoptotic inducing agents for cancer comprising any compound or its salt that inhibits the activity of any protein comprising the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, or comprising any compound that inhibits the expression of any gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or any partial peptide thereof.
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> The specification, prior art and claims do not adequately describe the broad genera of prophylactic, therapeutic and apoptotic compounds claimed. The specification teaches the detected overexpression of SEQ ID NO. 1 in various types of cancer cells or tissues, as well as teaching the cloning, recombinant expression using a full length construct, and siRNA inhibition of expression of SEQ ID NO. 1 in various cancer cells in vitro using a homologous siRNA construct. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genera comprising any compound that inhibits the activity of any protein with the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, nor do they indicate the attributes concisely shared by members comprising any compound that inhibits the expression of any gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or encoding any partial peptide thereof.
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> Nor does the specification describe elements which are essential to various functions claimed for each genus, and which provide for the functions claimed, or providing prophylactic, therapeutic or apoptotic inducing effects for any cancer. The specification does not place any limit on the number of nucleic acid or amino acid substitutions, deletions, insertions and/or additions that may be made within each genus claimed. The scope of the claims includes numerous structural variants, and each genus is highly variant because a significant number structural differences between genus members is permitted. Concise structural features that could

> distinguish compounds from others in each broad genus are missing from the disclosure.
>
> Furthermore, the specification fails to teach or adequately describe a representative number of species in each genus such that the common attributes or characteristics concisely identifying members of each proposed genus are exemplified. And the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed (e.g. what fragments of SEQ ID NO. 1 provide for the associated cancerous phenotype upon overexpression?). Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed genera, and because each genus is highly variant, the description provided for each genus is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera claimed. Thus, applicant was not possession of the claimed genera.".

Applicants respectfully disagree. As shown in the "Amendment of Claims", Applicants cancelled Claims 1, 2, 4, 6 and 18; amended Claim 3 to delete the phrases "substantially complementary", "substantially the same", and "partial peptide" and replace the phrase "represented by" with --of--; and amended Claim 19 to depend from Claim 3. Also, Applicants added new Claims 28-30. Support for the amendments can be found in original Claim 3, page 63, 64, Example 3, Example 5, and throughout the specification as originally filed. Applicants respectfully request reconsideration.

2. Claims 1-4, 6, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cloning, recombinant expression and siRNA inhibition of expression of SEQ ID NO. 1 in various cancer cells in vitro using homologous siRNA constructs, does not reasonably provide enablement for providing prophylaxis, treatment and apoptotic inducing effects for any cancer or cancer cell in an organism comprising any compound that inhibits the activity of any protein with the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, nor using any compound that inhibits the expression of any gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or encoding any partial peptide thereof. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Examiner states, "The claims are drawn to prophylactic/ therapeutic and apoptotic inducing agents for cancer or cancer cells comprising any compound or its salt that inhibits the activity of any protein comprising the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, or comprising any compound that inhibits the expression of any gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or any partial peptide thereof.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid prophylaxis and treatment or cancers in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo success. (A. Branch, Trends in Biochem. Sci. 23: 45-50; *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations...the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step

that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in sufficient amounts to effect a phenotype or desired effect in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic nucleic acids to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al, Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain... The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. ...it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." [references omitted].

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward methods of preventing any cancer, or of treating the broad genus of cancers claimed comprising any compound that inhibits the activity of any protein with the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, nor do they indicate the attributes concisely shared by members comprising any compound that inhibits the expression of any gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or encoding any partial peptide thereof.

The specification teaches detecting the overexpression of SEQ ID NO. 1 in various types of cancer cells or tissues, as well as teaching the cloning, recombinant expression of the full length construct, and siRNA inhibition of expression of SEQ ID NO. 1 in various cancer cells in vitro using a homologous siRNA construct. The specification and claims do not teach the use of the broad genera of compounds claimed, nor do they indicate what distinguishing attributes are concisely shared by the members of the genera comprising any compound that inhibits the activity of any protein with the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, nor do they indicate the attributes concisely shared by members comprising any compound that inhibits the expression of any

gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or encoding any partial peptide thereof.

One skilled in the art would not accept on its face the examples provided in the instant disclosure of the cloning, expression and siRNA mediated inhibition of SEQ ID NO. 1 as being correlative or representative of the ability to prevent and treat any cancer using the broad genera of compositions claimed in view of the lack of guidance in the specification and the known unpredictability associated with the ability to properly deliver adequate quantities of these inhibitory compounds to appropriate target cells in an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to prophylactic/ therapeutic and apoptotic agents for cancer comprising any compound or its salt that inhibits the activity of any protein comprising the substantially same sequence of SEQ ID NO. 1, or any partial peptide thereof, or comprising any compound that inhibits the expression of any gene encoding any substantially same amino acid sequence of SEQ ID NO. 1, or any partial peptide thereof.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the ability to prevent and treat a representative number of cancers in an organism using a representative number of species of each broadly claimed genus of compounds. Since the specification fails to provide any particular guidance for the successful prevention and treatment of a representative number of cancers using the compounds encompassed by the broad genera claimed, and since determination of the factors required for accomplishing these treatment and prophylactic effects is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Applicants respectfully disagree. The claimed subject matter recited in the amended claims relates to siRNA inhibition of expression of SEQ ID NO. 1 in various cancer cells in vitro using homologous siRNA constructs, which is acknowledged by the Examiner as being supported by the specification and enabling, and resulting apoptosis of the cells, for which support can be found in Example 3, Example 5 and the like. Applicants respectfully request reconsideration.

The rejections under 35 U.S.C. § 102/103 are overcome

3(a). Claims 1-4, 6, 18 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Isogai et al (USPN 6,943,241).

> The Examiner states, "Isogai et al (USPN 6,943,241) teach compounds that inhibit the expression and/or activity of a protein comprising the substantially same sequence encoded by SEQ ID NO. 1 or fragment thereof (see the abstract; col. 1-4, Table I, esp. col. 22, col. 78-81, SEQ ID NO. 3162 and the accompanying sequence alignment data). The burden of establishing whether the prior art compounds have the function of inhibiting gene expression or protein activity as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products." [footnote omitted] See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the compounds disclosed by Isogai et al meet all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of inhibiting expression of the target gene encoding SEQ ID No.1 and preventing, treating and inducing apoptosis of the cancers claimed.
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> Therefore, absent evidence to the contrary, claims 1-4, 6, 18 and 19 are anticipated' by or, in the alternative, obvious over Isogai et al.

3(b). Claims 1-4, 6, 18 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Jenuwein et at (USPN 6,689,583).

> The Examiner states, "Jenuwein et al (USPN 6,689;583) teach compounds that inhibit the expression and/or activity of a protein comprising the substantially same sequence encoded by SEQ ID NO.1 or fragment thereof (see the abstract; col. 1-4, 8-12, 13, 14, SEQ ID NO. 2 and the accompanying sequence alignment data). The burden of establishing whether the prior art compounds have the function of inhibiting gene expression or protein activity as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products." [footnote omitted] See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the compounds disclosed by Jenuwein et al meet all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of inhibiting expression of the target gene encoding SEQ ID No.1 and preventing, treating and inducing apoptosis of the cancers claimed.
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> Therefore, absent evidence to the contrary, claims 1-4, 6, 18 and 19 are anticipated by or, in the alternative, obvious over Jeuwein et al.".

3(c). Claims 1-4, 6, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Jenuwein et al (WO 96/35784).

> The Examiner states, "Jenuwein et al (WO 96/35784) teach compounds that inhibit the expression and/or activity of a protein comprising the substantially same sequence encoded by SEQ ID NO.1 or fragment thereof (see the abstract; Figure 7, claim 12, Accession NO. AAW05260 and the accompanying sequence alignment data). The burden of establishing whether the prior art compounds have the function of inhibiting gene expression or protein activity as claimed falls to applicant. See (In re Best, 562

> F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products." [footnote omitted] See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the compounds disclosed by Jenuwein et al meet all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of inhibiting expression of the target gene encoding SEQ ID No.1 and preventing, treating and inducing apoptosis of the cancers claimed.
>
> Therefore, absent evidence to the contrary, claims 1-4, 6, 18 and 19 are anticipated by or, in the alternative, obvious over Jeuwein et al.".

Applicants respectfully disagree. The amended Claim 3 recites "an antisense polynucleotide comprising the entire or part of a base sequence complementary to a base sequence of a polynucleotide encoding a protein having the amino acid sequence of SEQ ID NO: 1". As a backup of Claim 3, Claim 28, which does not recite the partial sequence, and Claim 29, which recites the specific siRNA sequences used in Example 3 and Expense 5, have been added. Claim 30, which is directed to an apoptosis inducing agent and indirectly depend from Claims 28 and 29, is also added. As such, the claims of the present inventions are novel and non-obvious in view of Isogai and/or Jenuwein. Applicants respectfully request reconsideration.

Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the Section 112 and 102/103 rejections of amended

claims 3 and 19, as well as new claims 28-30. Claim 3 is described, enabled, novel and non-obvious for at least the reasons given above. Claims 19 ultimately depend from claim 3, and is thus, also described, enabled, novel and nonobvious for at least the same reasons noted above for claim 3.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

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Respectfully submitted,

By _____

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